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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,034	06/15/2006	Philippe Gauthier	P08951US00/BAS	6756

881 7590 09/10/2008

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
09/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,034	GAUTHIER ET AL.	
	Examiner	Art Unit	
	ANNE L. HOLLERAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7 and 8* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I (claims 1-8) in the reply filed on 5/16/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 does not begin with an article. Appropriate correction is required.

Claims 5 and 6 are objected to for a typographical error: "aminoacid", which should be corrected to "amino acid".

Claims 1-15 are pending.

Claims 9-15, drawn to non-elected inventions, are withdrawn from consideration.

Claims 1-8 are examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of the phrase "antibody Fab or scFv fragment", because it is not clear if this means a fragment of either an antibody Fab or scFv, or alternatively, a fragment of an antibody, where the fragment is a Fab or scFv. If applicant intends the latter, the inclusion of a hyphen after "Fab" and "scFv" would obviate this rejection.

Claim 1 is further indefinite because of the phrase "characterized by the ability to mimic Her-2/neu tumor associated antigen", because this is not a positive recitation of the function of mimicking Her-2/neu. Therefore, it is not clear if the claim is limited to those species which in fact mimic Her-2/neu.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for anti-idiotypic antibody Fabs or scFvs that mimic Her-2/neu, such as scFv40 comprising SEQ ID NO: 1, or scFv69, comprising SEQ ID NO: 2, does not reasonably provide enablement for fragments of anti-idiotypic antibody Fabs or scFvs, or for scFvs or Fabs where only one CDR is defined, such as the fragments of claims 2 and 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation

necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claimed invention is drawn to anti-idiotype antibody fragments (Fab or scFv), or to fragments of Fab or scFv immunoglobulins that mimic Her2, a tumor antigen. Anti-idiotype antibodies are antibodies that bind to the antigen binding site of a first antibody (Ab1), in the present case, an anti-Her2 antibody such as trastuzumab. An anti-idiotype antibody may be used instead of an antigen to generate an antibody response (Ab1') against a tumor antigen.

The specification provides no direction or guidance regarding how to produce the human Fab or scFv immunoglobulins as broadly defined by the claims, because the specification fails to teach how to make Fab or scFv immunoglobulins with the requisite binding specificity and affinity where the Fab or scFv comprise a V_H domain and V_L domain where only CDR3 of each domain is defined. The specification teaches how to make human antibody fragments from phage display libraries, by panning the ETH-2 scFv library with trastuzumab $F(ab')_2$ fragments. Anti-Id scFv were characterized by ELISA experiments using HER-2/neu ECD-Fc fusion protein to inhibit the binding of soluble scFv to trastuzumab $F(ab')_2$ fragments or purified scFv was used to block the binding of HER-2/neu ECD-Fc fusion protein to Ab1. Selected three scFv fragments termed scFv 39, 40 and 69, which recognize the binding site of Ab1 but exhibit different random loops of five or six amino acids in CDR3 of the V_H and V_L domains (SEQ ID NOS: 7-12 are sequences of CDR3s for heavy and light chains of each of the three scFvs; page 23). While the specification teaches three examples of anti-idiotype scFv that bind to

trastuzumab, and provides the amino acid sequence of each antibody, the specification provides no demonstration that individual CDR3 sequences are solely responsible for binding to trastuzumab, or that the residues within CDR1 or CDR2 may be changed without affecting binding, or that pairs of CDR3s may be placed into frameworks with CDR1 and CDR2 sequences that are different from those found in the parent scFv molecules. Therefore, the specification fails to teach the critical residues required for binding activity.

While the level of skill of those in the antibody arts is high, unpredictability is found in the antibody arts. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff (*Rudikoff et al, Proc Natl Acad Sci USA 1982 Vol 79 page 1979*). Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Furthermore, while there are some publications that acknowledge that CDR3 is important, the conformations of other CDRs as well as the framework residues influence binding. For example, MacCallum *(MacCallum et al, J. Mol. Biol. (1996) 262, 732-745)* analyzes many different antibodies for interactions with antigen and states that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). De Pascalis *(De Pascalis et al, The Journal of Immunology (2002) 169, 3076-3084)* demonstrates that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding

site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *(Casset et al, (2003) BBRC 307, 198-205)*, which demonstrates the construction of a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design, where the peptide has 27 residues formed by residues from 5 CDRs (see entire document). Casset also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.). This is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Vajdos (*Vajdos et al. J. Mol. Biol.(2002) 320, 415-428)*, summarizes the generally known relationship between antibody structure and antigen binding, i.e. that antigen binding is primarily mediated by the CDRs in an antibody Fv, while more highly conserved framework segments that connect the CDRs are mainly involved in supporting the CDR loop conformations, but in some cases framework residues also contact antigen (page 416, left col.). Additionally, Vajdos suggest that an important step for understanding how a particular antibody functions, it would be useful to assess the contributions of each CDR side chain to antigen binding, and in so doing produce a functional map of the antigen-binding site. In the present case, this is a step that has not been demonstrated by the disclosure of the instant specification for any of the exemplified monoclonal antibodies. Furthermore, Holm (*Holm et al Mol. Immunol., (2007) 44, 1075-1084)* describes the mapping of an anti-cytokeratin antibody where, although residues in the CDR3 of the heavy chain are involved in antigen binding, unexpectedly a residue in CDR2 of the light chain was

also involved (abstract). Chen (*Chen et al. J. Mol. Biol. (1999) 293, 865-881)* describes high affinity variant antibodies binding to VEGF where the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu (*Wu et al. J. Mol. Biol. (1999) 294, 151-162)* state that, while certain residues have been identified as important for maintaining conformation, it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.).

In summary, while there may be examples in the art where substitutions in CDRs or in the frameworks have been made and antigen-binding activity is maintained, these substitutions appear to be different for each antibody on a case-by-case basis. Therefore, because the specification lacks any teachings showing examples of antibodies where CDRs have substituted one for another between different monoclonal antibodies, where substitutions have been made anywhere with a heavy and/or a light chain of a given antibody, or where a heavy chain from one antibody has been paired with a light chain from another antibody, one of skill in the art would have to engage in further and undue experimentation to practice the full scope of the claimed invention. The further experimentation would be undue experimentation because, as discussed above, it is not at all clear that for the given antibodies described in the specification as originally filed, that the sequence of the CDR3 is the sole critical element for binding to trastuzumab.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baral (Baral, R. et al., Int. J. Cancer, 92: 88-95, 2001; cited in the IDS), in view of Fengtian (Fengtian, H. et al., Chin. Med. Sci. J. 17(4): 215-219, 2002; of record) or Tripathi (Tripathi, P.K., et al., Molecular Immunology, 35: 853-863, 1998), and further in view of Marks (Marks, J.D. et al., J. Mol. Biol., 222(3): 581-597, 1991; of record).

Baral teaches an murine anti-idiotypic monoclonal antibody that binds to the 520C9 murine anti-Her2 antibody, and that functionally mimics the human Her2/neu epitope (see abstract; page 89, left column). Baral teaches a pharmaceutical composition comprising an anti-

idiotypic antibody in association with a pharmaceutically acceptable carrier, Freund's adjuvant (se page 89, left column). Baral fails to teach an anti-idiotypic human Fab or scFv immunoglobulin. However, methods of generating phage-displayed anti-idiotypic antibody scFv directed against a monoclonal antibody directed against a tumor antigen are known in the art as evidenced by the teachings of Fengtian (see abstract) or Tripathi (see abstract). Fengtian also teaches that using phage display to generate anti-idiotypic scFv directed against an antibody simplifies the process of making anti-idiotypic antibodies (see page 216, left column). Tripathi teaches an alternative method of making an anti-idiotypic scFv immunoglobulin, because Tripathi's scFv immunoglobulin is made by isolating the mRNA that encodes the heavy and light chains of the anti-idiotypic antibody, 3H1 (see page 854, left to right columns). Neither Fengtian nor Tripathi teaches the making of human scFv immunoglobulins. However, libraries for making human scFv fragments are known in the art as evidenced by the teachings of Marks (Marks, J.D. et al., J. Mol. Biol., 222(3): 581-597, 1991; see abstract). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a human scFv anti-idiotype immunoglobulin directed against an anti-Her2/neu antibody, because anti-Her2 antibodies are known in the art, use of phage display for generating scFv immunoglobulins that bind to antibodies is known in the art, and because libraries for making human scFv immunoglobulins are known in the art. One would have been motivated to make a human scFv immunoglobulin instead of a murine, intact anti-idiotypic antibody because the antigenic response directed against a human scFv will be directed toward the generation of antibodies that bind to the antigen binding site (generation of Ab3).

Claims 1, 4 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baral (Baral, R. et al., Int. J. Cancer, 92: 88-95, 2001; cited in the IDS), in view of Fengtian (Fengtian, H. et al., Chin. Med. Sci. J. 17(4): 215-219, 2002; of record) or Tripathi (Tripathi, P.K., et al., Molecular Immunology, 35: 853-863, 1998), in view of Marks (Marks, J.D. et al., J. Mol. Biol., 222(3): 581-597, 1991; of record), and further in view of Cho (Cho, H.-S. et al., Nature, 421: 756-760, 2003, February).

Claim 4 is drawn to a human anti-idiotypic Fab or scFv that mimics Her-2/neu tumor associated antigen and is directed against trastuzumab F(ab')2.

Baral, Fengtian, Tripathi and Marks teach as set forth above. The combination of Baral, Fengtian, Tripathi and Marks fails to teach an anti-idiotypic Fab or scFv that is directed against trastuzumab. However, trastuzumab (Herceptin®) is known in the art as a therapeutic antibody useful in the treatment of breast cancer (see page 758, right column). Furthermore, the specific epitope that is bound by trastuzumab (Herceptin® binding site) appears to be known and is taught by Cho to be a site that, when bound by an antibody allows the crosslinking of Her2 receptor and the inhibition of Her2 activation that occurs after proteolytic cleavage (see page 758-759, bridging paragraph). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used trastuzumab as the Ab1 in making an anti-idiotypic Fab or scFv as encompassed by the claims, because trastuzumab is known in the art and available, and because the epitope that is bound by trastuzumab appears to be involved in the activation of Her2 function.

Claims 1, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baral (Baral, R. et al., Int. J. Cancer, 92: 88-95, 2001; cited in the IDS), in view of Fengtian (Fengtian, H. et al., Chin. Med. Sci. J. 17(4): 215-219, 2002; of record) or Tripathi (Tripathi, P.K., et al., Molecular Immunology, 35: 853-863, 1998), in view of Marks (Marks, J.D. et al., J. Mol. Biol., 222(3): 581-597, 1991; of record), and further in view of Todorovska (Todorovska, A. et al., Journal of Immunological Methods, 248: 47-66, 2001).

Claim 7 is drawn to a multimer of the antibody fragment defined in claim 1.

Baral, Fengtian, Tripathi and Marks teach as set forth above. The combination of Baral, Fengtian, Tripathi and Marks fails to specifically teach a multimer of the antibody of claim 1. However, Todorovska reviews methods for making dimeric and multimeric species of scFv immunoglobulins, and teaches that such multimeric species have increased biding valency leading to increased affinity, and as well such multimeric species allow crosslinking of antigens (see Todorovska, pages 48-49). Additionally, the increased size of multimeric species will minimize the rapid, first-pass clearance from circulation (see page 56 of Todorovska, left column), which would allow a higher concentration of scFv to be available as antigen when used in for in vivo therapy purposes. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Baral, with Fengtian or Tripathy, with Marks, and with Todorovska to make multimeric human anti-idiotypic Fab or scFv fragments that mimic the Her2/neu antigen, because the methods for making multimeric species were known in the prior art, and one would have been motivated by the goal of decreasing the clearance of the scFv from circulation.

Conclusion

No claim is allowed. Claims 5 and 6, which are free of the art, are objected to for being dependent from rejected claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
September 4, 2008

/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643